REMARKS / ARGUMENTS

Claims 74-84 are under consideration and are presently rejected. Claims 85-93 are withdrawn.

Claims 74 and 75 have been amended and new claim 94 has been added. Basis for the amendment to claim 74 is found in US2001/0053365A1 (the publication of the application) in paragraph [0023] and also claim 5 as filed. Basis for the amendment to claim 75 is found in US2001/0053365A1 (the publication of the application) in paragraph [0024]. Basis for new claim 94 is found in US2001/0053365A1 (the publication of the application) in paragraph [0027].

Objection under 35 USC s103

Examiner has alleged that claims 74-84 are unpatentable over Lipford (Vaccine 1994 12(1) 73-80) in view of the teachings of Kensil (US 5583112). .

The Examiner explains that Lipford teaches the making of an immunogenic composition comprising 5mg of cholesterol and 0.4mg of Quil A and that the ratio of cholesterol to Quil A is 12.5:1, and the Examiner correctly points out that Lipford does not teach the use of purified QS21. Additionally the Examiner states that Lipford teaches there are two aspects of ISCOMs important to their activity-the liposome structure and the adjuvant properties of Quil-A. (page 5)

The Examiner also discusses Kensil, which the Examiner notes teaches QS-21 as a component of Quil-A. The Examiner also states that Kensil teaches that purified saponins show adjuvant effects at lower dosages than crude saponin extract and tend to be less toxic (have less hemolytic activity) than the Quil A extract. Kensil also indicates that the ISCOM properties identified for Quil A are also indicative of saponins in general. According to the Examiner, this suggests fractions of QuilA, like QS21, would share the required properties.

The Examiner concludes, therefore, that for these reasons it would be obvious to a person of ordinary skill in the art to substitute QS21 ,which is one of the purified saponins of Kensil, for the crude Quil A extract used in Lipford.

With respect, Applicants traverse the rejection. The evidence at the priority date was that QS21 was not capable of forming ISCOMs using known techniques without the concurrent presence of other components from Quil A, as explained below. At the time of filing, it would not have been obvious for one skilled in the art to combine the teachings of Lipford and Kensil to conclude that the ISCOMs of Lipford could be made more safe and effective by replacing Quil A with purified QS21.

ISCOMs were first described by Morein in Nature (1984) 308, 457-460. His method of producing them involved solubilising cholesterol and Quil A in water in the presence of a high concentration of detergent, followed by a step to remove sufficient detergent from the formulation to allow the ISCOMs to form. Ozel in J Ultrastructure and Molecular Structure Research (1989) 102, 240-248 uses this technique to form Quil A ISCOMs be extracting the detergent (in this case MEGA-10) by dialysis. However in later years before the present application was filed a number of authors published work showing that pure QS21 could not form ISCOMs using the known techniques of Ozel and Morein. One piece of evidence for this is WO90/03184. QS21 is identified in this document as "B2" as shown by the fact that both QS21 and B2 are pure fractions of Quil A that have a molecular weight of 1988. On page 30 lines 4-5 of WO90/03184 it is stated that "B2 does not form ISCOM-like structures with cholesterol but binds to cholesterol". In the next sentence it goes on to say that another Quil A fraction ("B2B") is required before QS21 can form part of an ISCOM. A second piece of evidence is WO92/06710 which describes the production of ISCOMs using fractions of Quil A (including QS21) and discusses WO90/03184 and the fact that QS21 does not form ISCOMs. On page 2 of WO90/03184 it is stated that: "B2 and B3..., which do have adjuvant activity, form a bond with cholesterol but do not form an ISCOM-like structure therewith." Also in the examples section the authors of WO92/06710 failed to make ISCOMs containing pure QS21 (page 19, table D, using a 4 hour dialysis step (described on page 11)) where the particle size produced was ">1000nm" when we know that the particle diameter of ISCOMs is around 40nm.

Hence the person skilled in the art at the priority date thought that pure QS21 would not form ISCOMs. He would therefore not be motivated by the teachings of Kensil to replace the Quil A in the formulations of Lipsford with substantially pure QS21, since

Lipsford teaches to produce ISCOM formulations. Moreover, given the state of the art at the time of filing, a person of ordinary skill in the art attempting such a combination would not have a reasonable expectation of success.

Applicants also respectfully submit that the Examiner's characterization of Kensil's teachings implies (i) QS21 had greater adjuvant potency than Quil A and (ii) QS21 exhibits lower hemolysis than Quil A. Applicants note that neither implication is correct.

With respect to this fist implication, statements made in col 6 and cols 22-23 of Kensil mention that QS21 has an adjuvant effect, however Kensil does not present any side by side comparison which would allow it to be concluded that QS21 has greater adjuvant potency than Quil A. It is true that in the section spanning columns 3 and 4 it is said that "The substantially pure adjuvants of the present invention are useful as immune adjuvants and enhance immune responses in individuals at much lower concentrations than the previously available heterogeneous saponin preparations ...". However there is no basis for deducing from this general statement concerning purified fractions that it is true in specific terms in respect of QS21. For example the adjuvant potencies of many of the fractions of Quil A are shown in Table 2 in col 14 but QS21 is not even listed in this table.

With respect to the second implication, Kensil states in cols 3-4 "The substantially pure adjuvants of the present invention are useful as immune adjuvants ...without the toxic effects associated with crude saponin preparations ..." and the reference in col 20 to the "toxic component QS-19". However once again this is a general statement which does not give support for any deduction that QS21 is a substance which lacks toxic effects. It is true that Quil A has a greater liver toxicity than QS21, presumably because Quil A contains the toxic compound QS-19 (see Example 16, col 27). However in fact QS21 is not said to be any less haemolytic than Quil A (see col 20 lines 37-38) and Figure 12 which shows that Quil A and QS21 are basically equivalent in terms of hemolysis. The substances that are least haemolytic are QS7 and QS8.

The general statements in Kensil regarding the properties of purified fractions of Quil A provides no basis to conclude that QS21 is a safer and more effective replacement

as an adjuvant for Quil A. Hence a skilled person would not on the basis of Kensil replace Quil A in the formulations of Lipford with substantially pure QS21.

In light of the above arguments, Applicants request that the Examiner withdraw the rejection and favourably reconsider the claims as presented.

Respectfully submitted,

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